Alcohol: How does it Do the Things it Does? A Neurobiological Perspective

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National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. In: Sullivan EV, Pfefferbaum A (eds) Alcohol and the Nervous System (series title: Handbook of Clinical Neurology, vol. 125). Elsevier, Amsterdam, 2014, pp. 33-54.

Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology Reviews 35 (2010) 217-238

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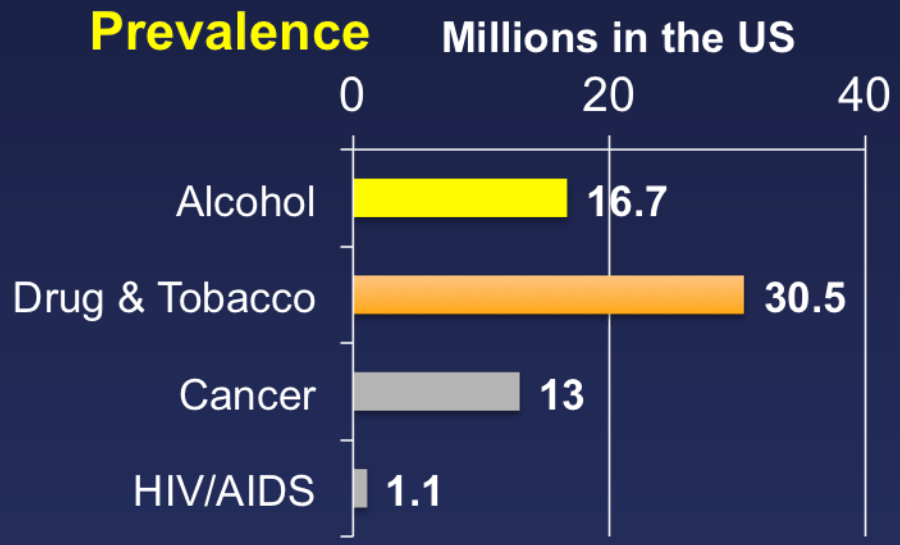
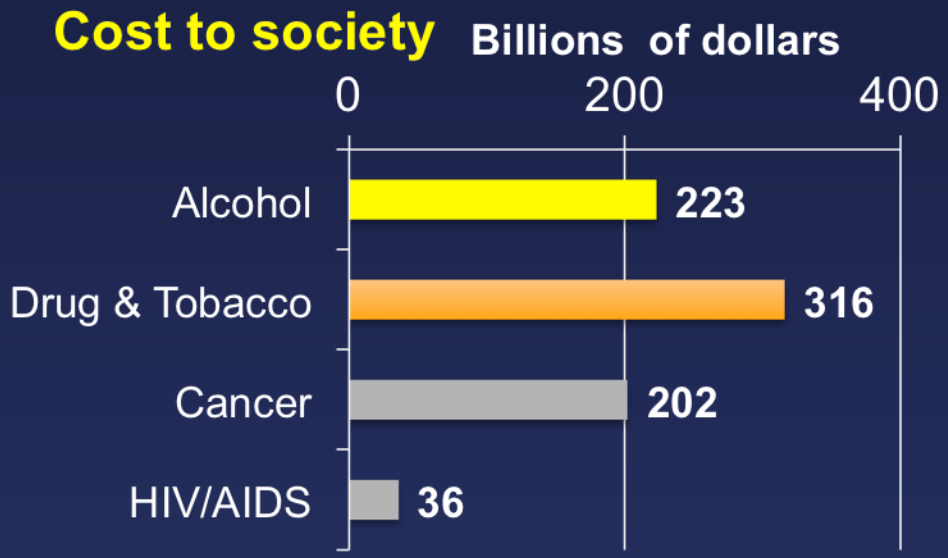
Cost and Scope of Addiction





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Addiction

Addiction — Defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take drug or stimulus, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug or stimulus is prevented (here, defined as the "dark side" of addiction)

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Bottom Line

1. Addiction is an incentive salience disorder

2. Addiction is a reward deficit disorder/ Addiction is a stress surfeit disorder

4. Addiction is an executive function disorder

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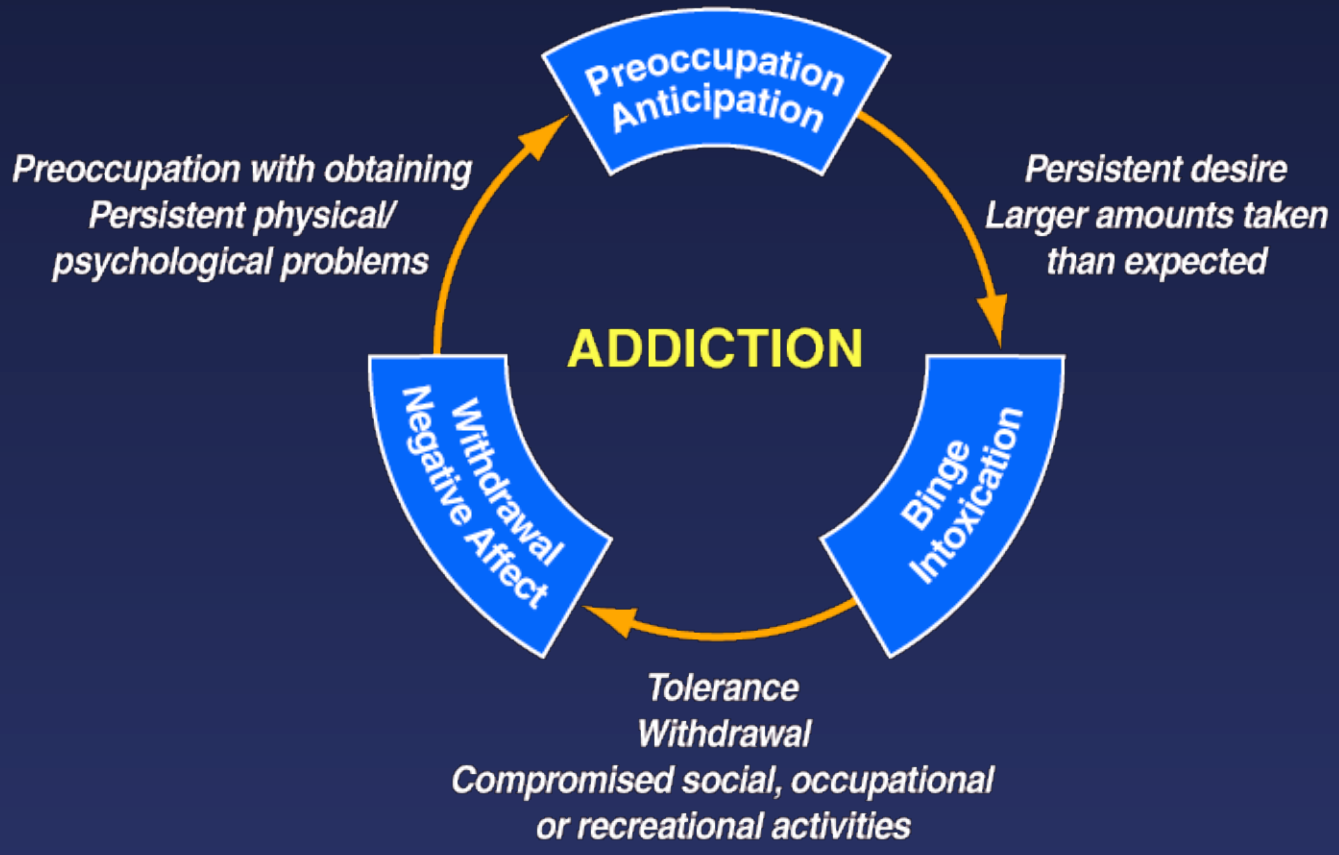
Stages of the Addiction Cycle



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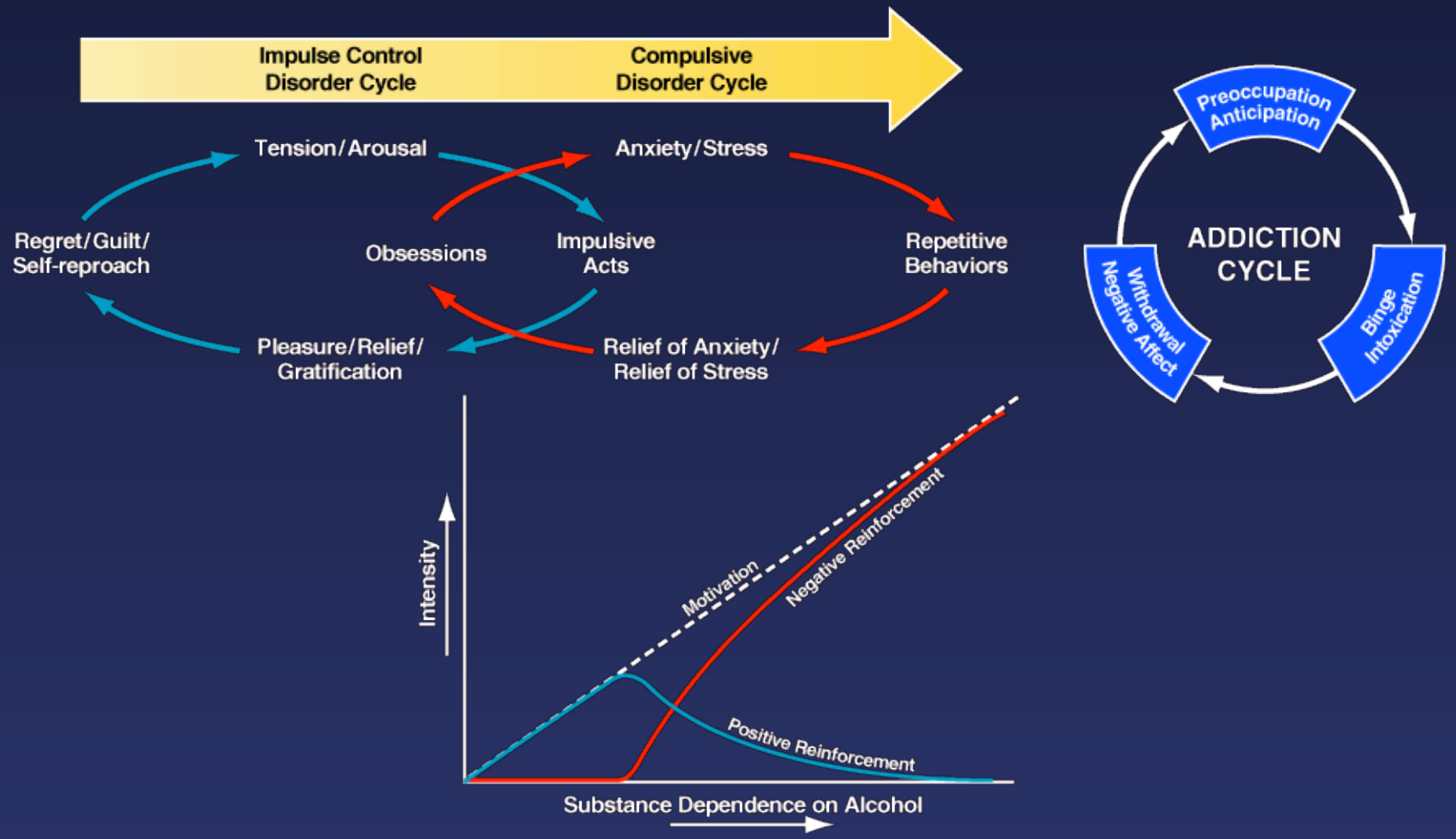
Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking



From: Koob GF. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. In: Spanagel R, Sommer W (eds) Behavioral Neurobiology of Alcohol Addiction (series title: Current Topics in Behavioral Neuroscience, vol 13), Springer, New York, pp 3-30.

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Positive and Negative Reinforcement - Definitions

Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug taking paradigms).

Negative Reinforcement — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)

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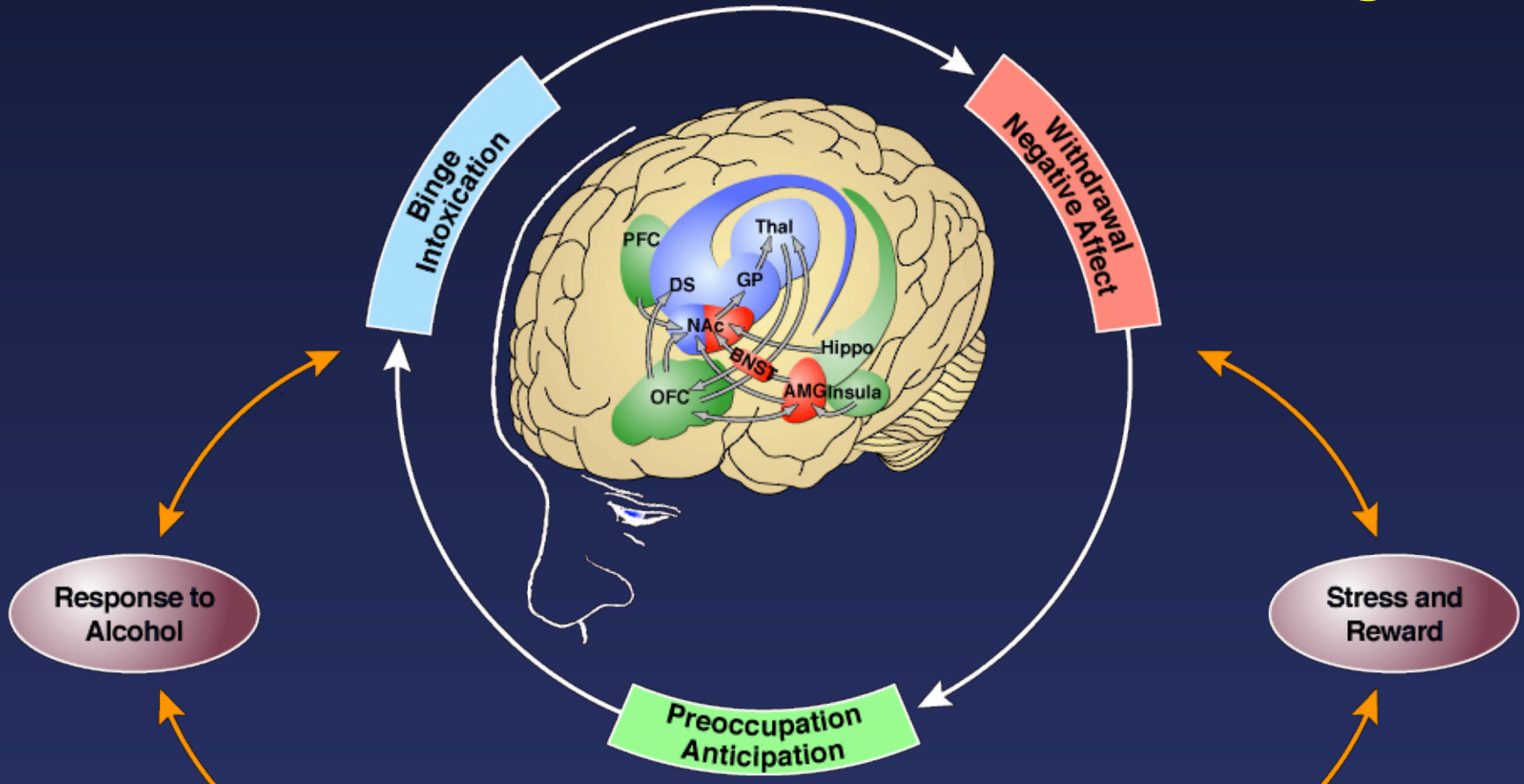
Conceptual Framework for Neurobiological Bases of the Transition to Excessive Drinking



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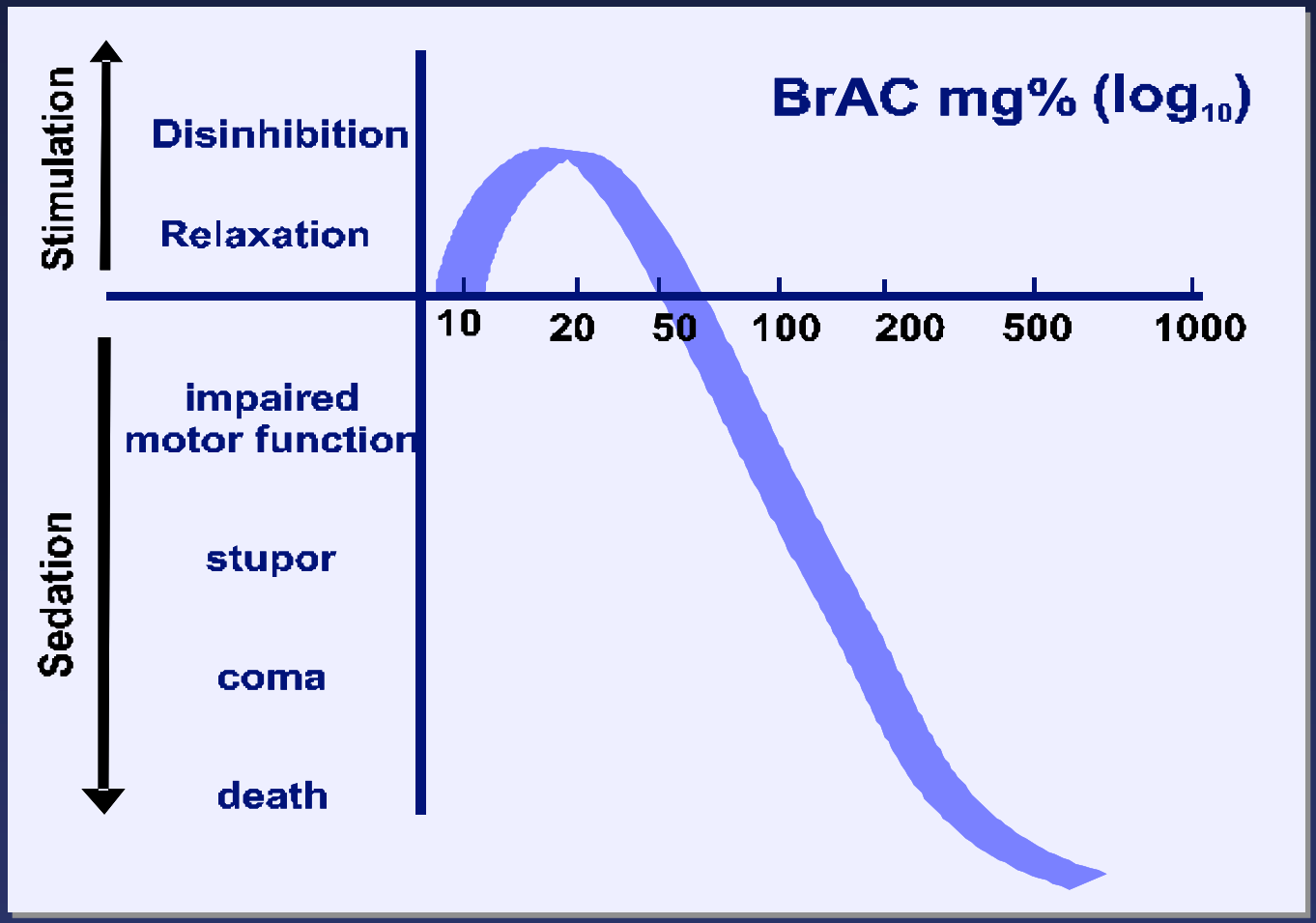
Behavioral Effects of Alcohol Related to Blood Alcohol Level in mg%

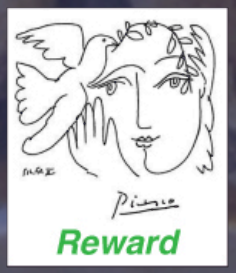


Stress and Reward: The Two Faces of Janus

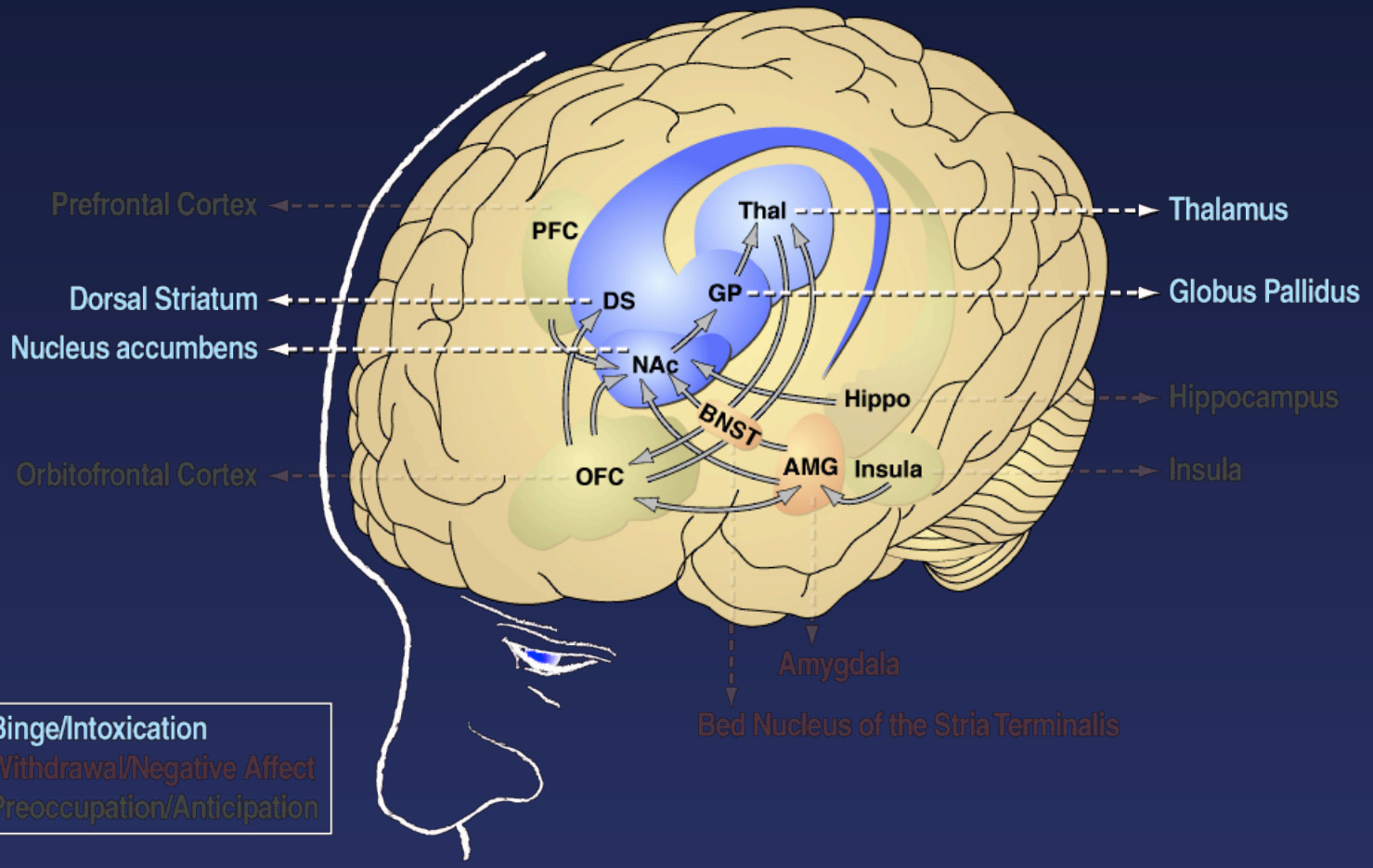
- Reward and stress resemble the Roman God Janus.
- Janus was the god of doors, passages and transitions and his two faces look to the future and the past.
- Reward and stress represent different components of transitions in our brain emotional systems that lead to and perpetuate addiction.

"Stress is anything which causes an alteration of psychological homeostatic processes"
from: Burchfield SR, Psychosom Med, 1979, 41:661-672.

Reward is defined as a stimulus (drug) that increases the probability of a response, but usually includes a positive hedonic connotation



Neural Circuits of the Binge/Intoxication Stage



Incentive Salience

- euphoria
- intoxication
- cue learning
- habits

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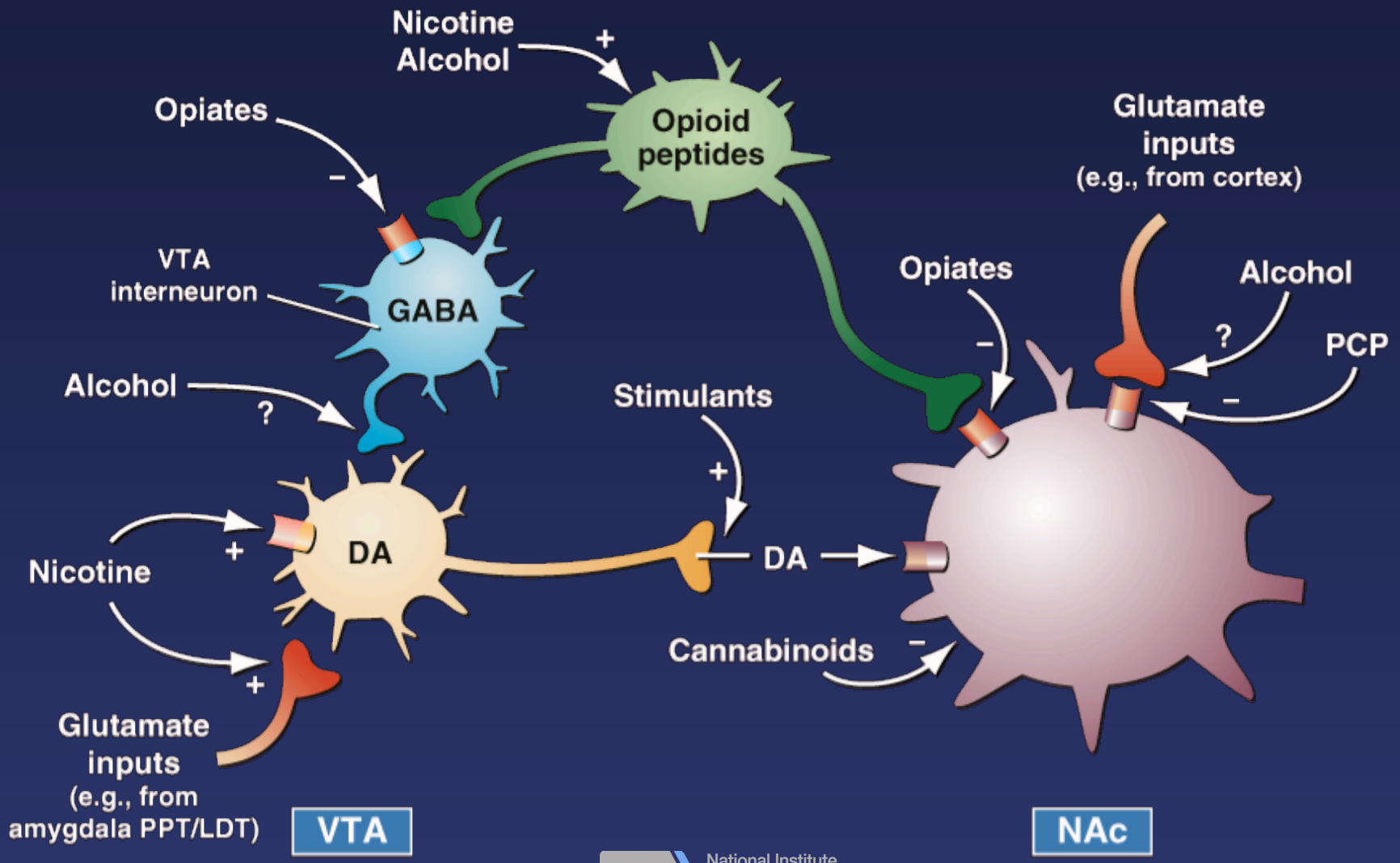
From: Koob GF, Volkow ND. Neuropsychopharmacol Rev, 2010, 35:217-238.

Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens



From: Nestler EJ, Nat Neurosci, 2005, 8:1445-1449.

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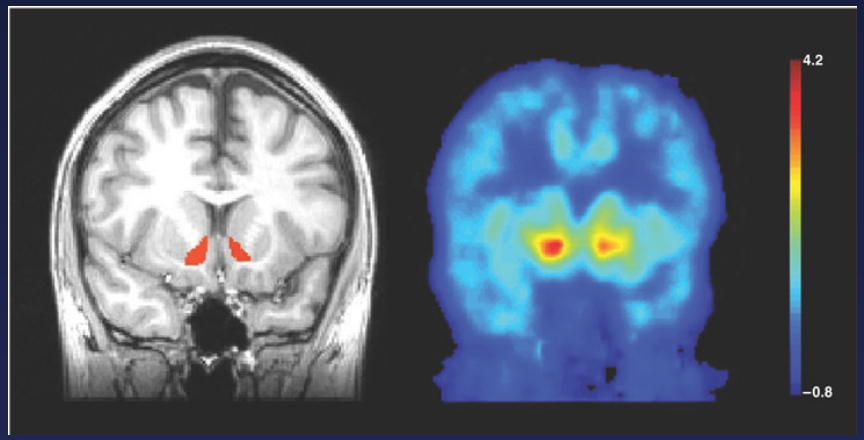
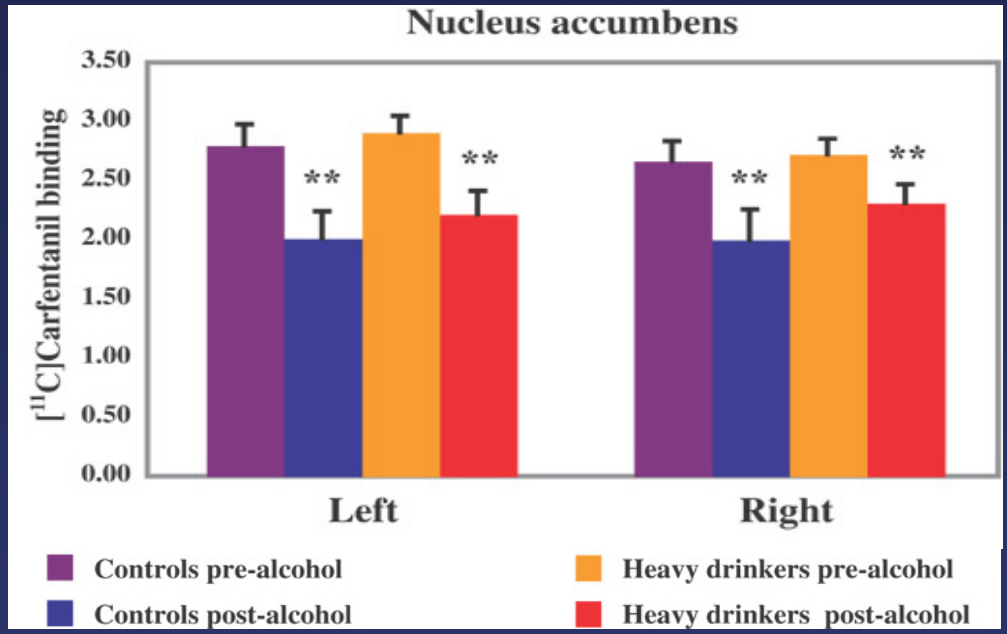
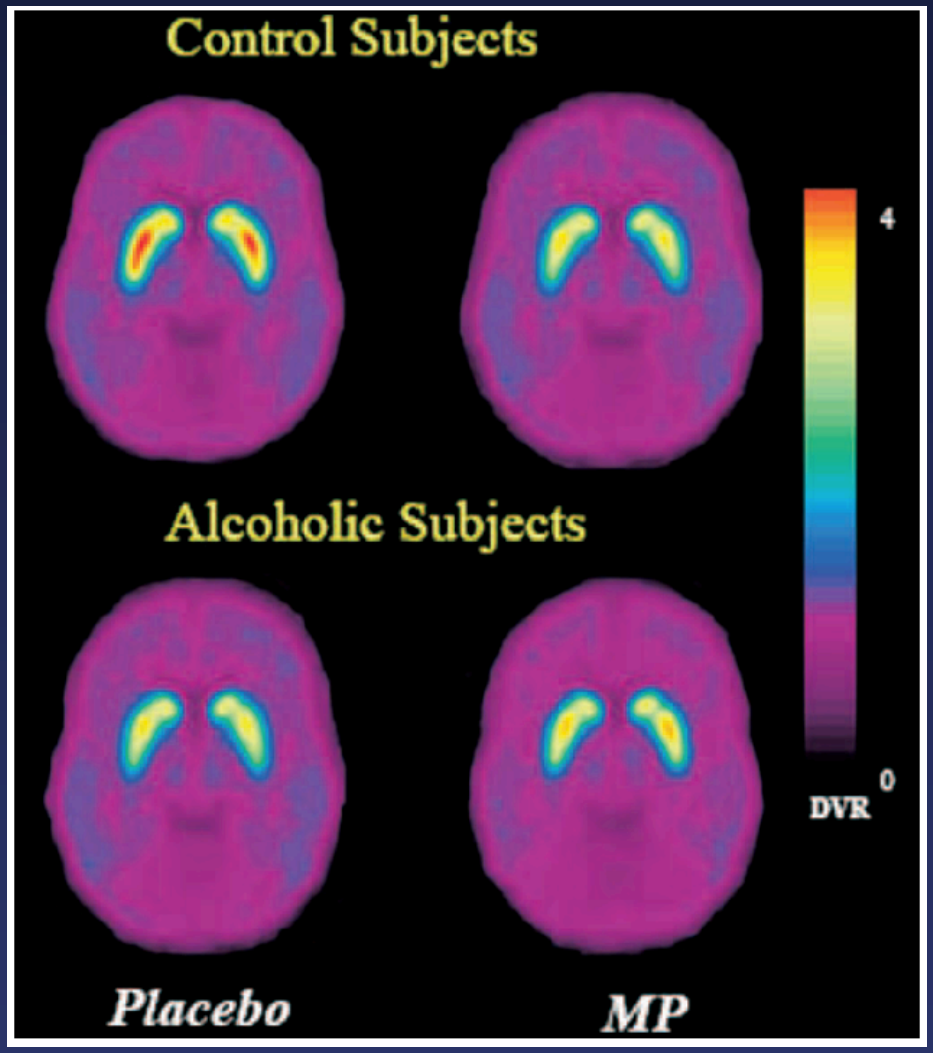
Reward Neurotransmitter Release by Alcohol-Alcohol Consumption Induces Endogenous Opioid Release in the Human Nucleus Accumbens





From: Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. Sci Transl Med, 2012, 4:116ra6.

Decreased Methylphenidate-induced Dopamine Release in Striatum of Alcoholics



From: Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Jayne M, Ma Y, Pradhan K, Wong C. J Neurosci, 2007, 27:12700-12706.

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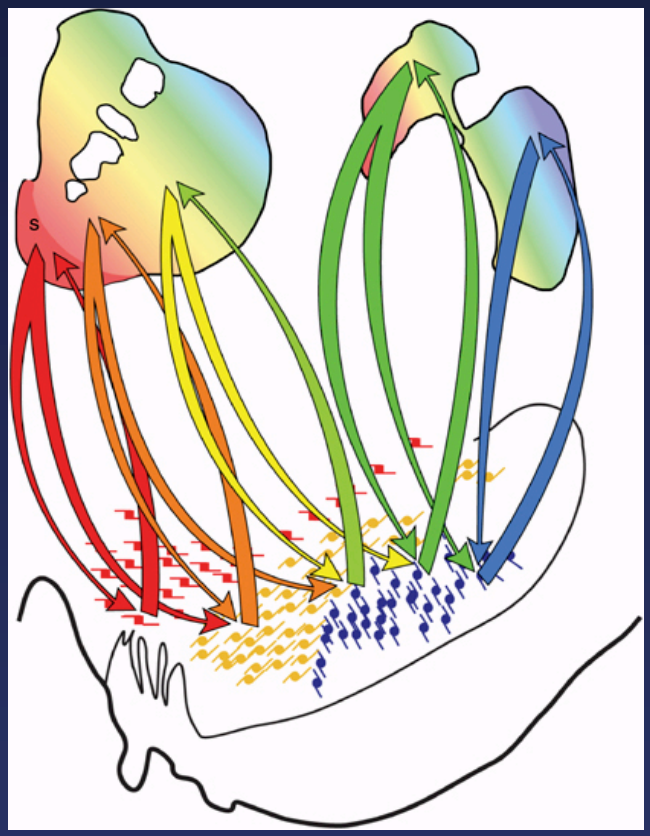
The Ventral-to-Dorsal Striatal Shift: Ascending Spirals from Shell to Core to Dorsal Striatum via Striato-VTA/Nigrostriatal Pathways

Everitt BJ, Robbins TW.
Nat Neurosci, 2005, 8:1481-1489



Haber SN, Fudge JL, McFarland NR.
J Neurosci, 2000, 20:2369-2382

Similar organization in rat brain:
Ikemoto S. Brain Res Rev, 2007, 56:27-78.

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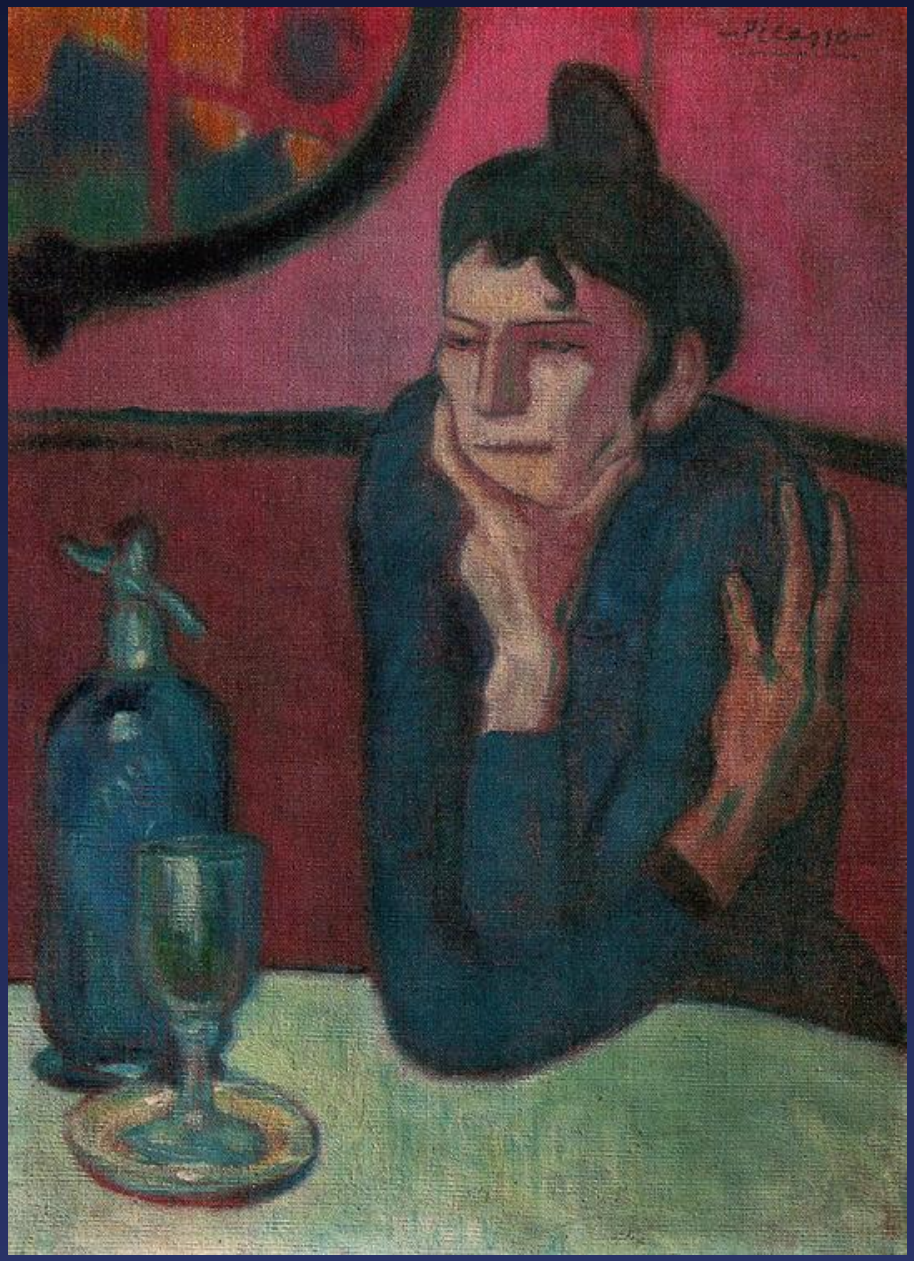

"Absinthe Drinker"
Pablo Picasso (1910)

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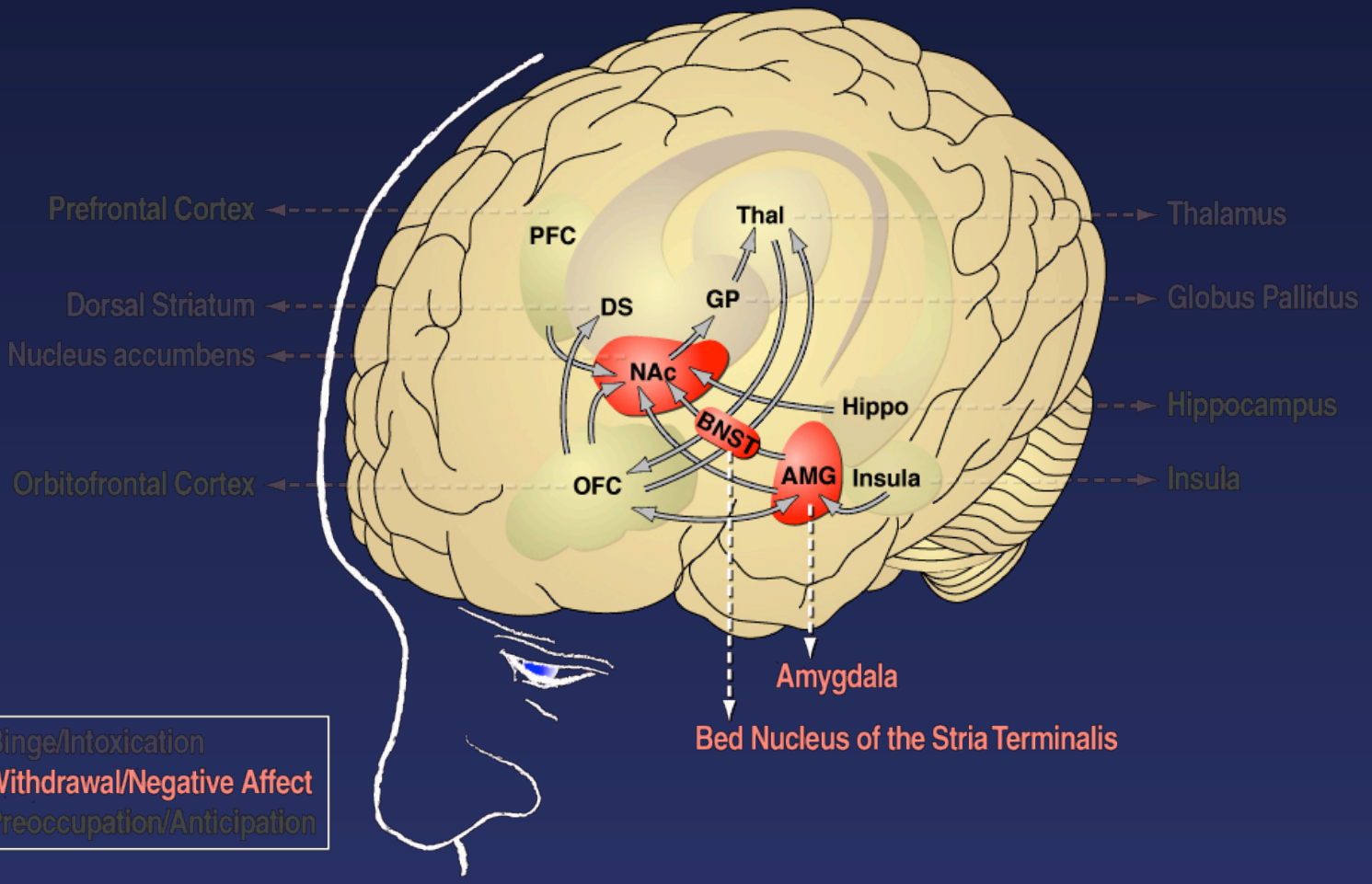
Neural Circuits of the Withdrawal/Negative Affect Stage



Negative Affect

- dysphoria
- anxiety
- irritiability
- malaise

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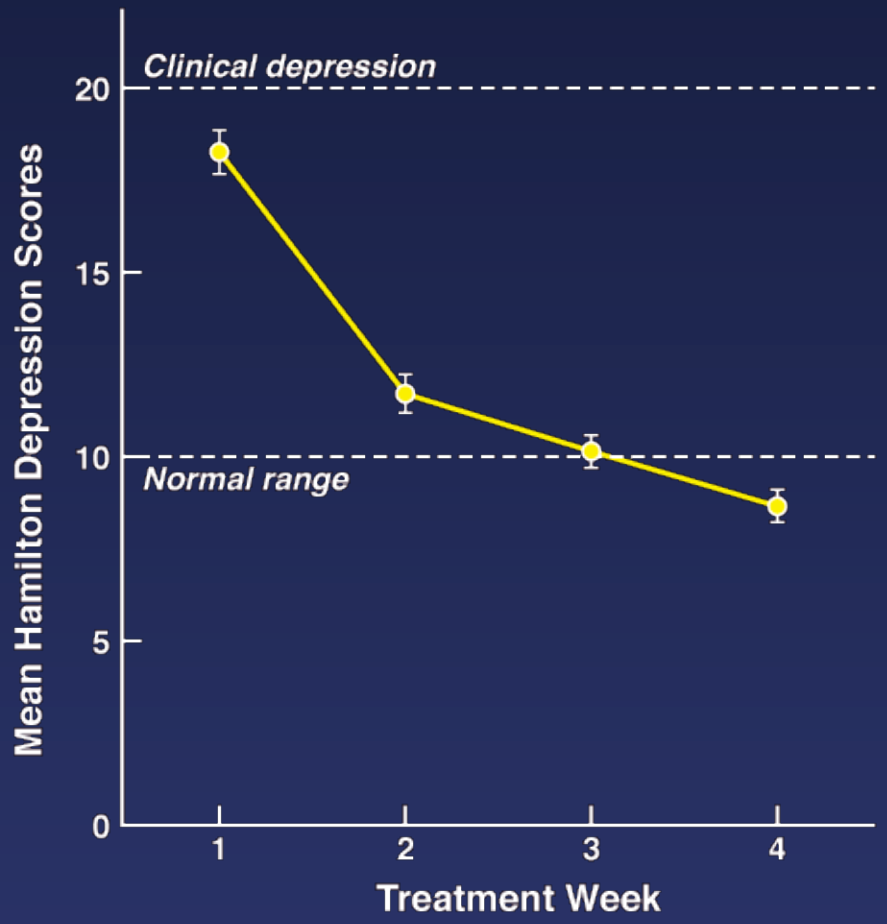
Withdrawal-induced Negative Affect- Hamilton Depression Scores in Male Primary Alcoholics During 4 Weeks of Abstinence



From: Brown SA, Schuckit MA. J Stud Alcohol, 1988, 49:412-417.

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects

- ↑ Dopamine
- ↑ Opioid peptides
- ↑ Serotonin
- ↑ GABA

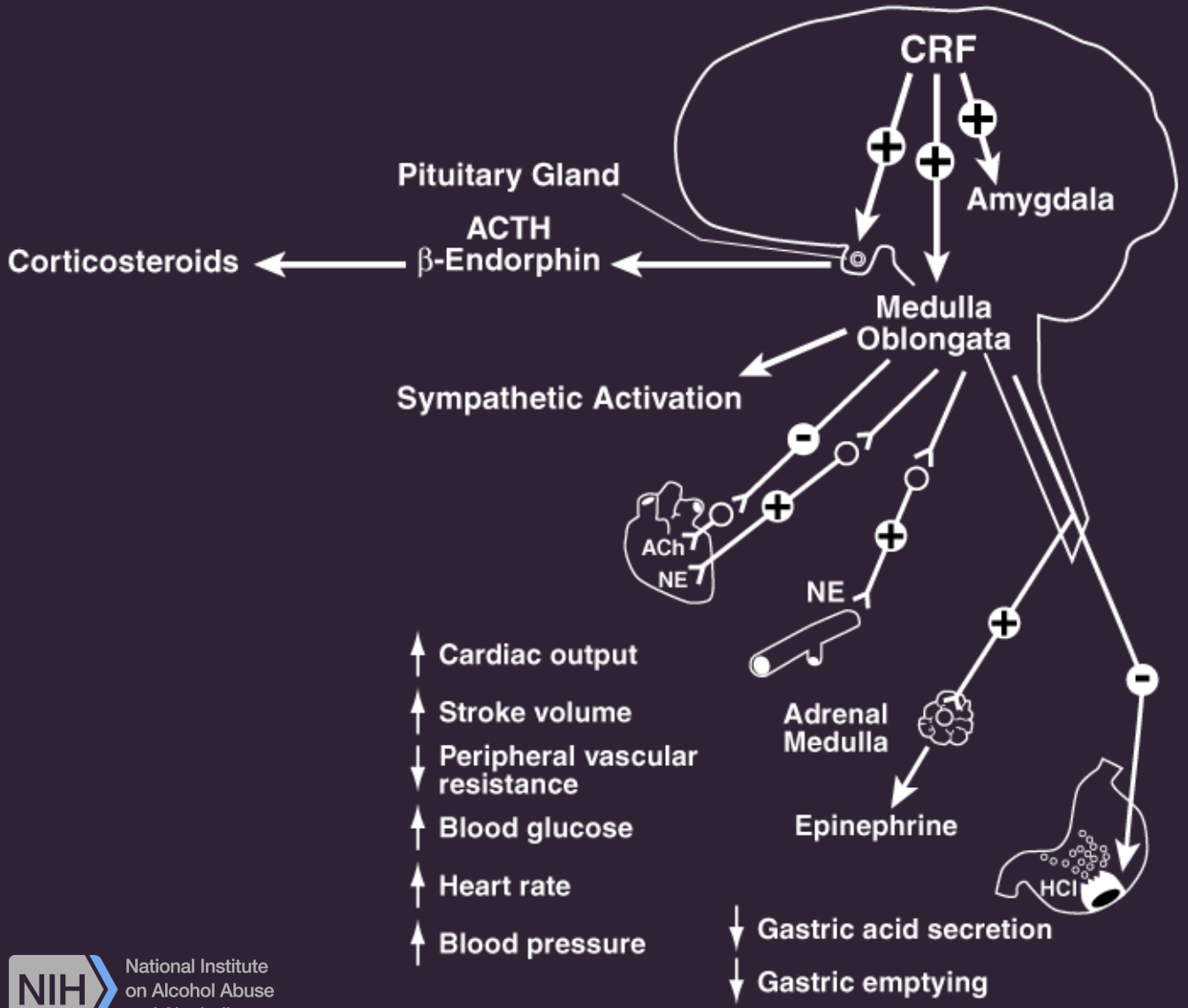
Negative Hedonic Effects of Withdrawal

- ↓ Dopamine … “dysphoria”
- ↓ Opioid peptides ... pain
- ↓ Serotonin … “dysphoria”
- ↓ GABA … anxiety, panic attacks

Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

- ↑ CRF … stress
- ↑ Dynorphin … "dysphoria"
- ↑ Vasopressin…. Stress
- ↑ Norepinephrine … stress

Brain Actions of Corticotropin-Releasing Factor (CRF)



Prof. Wylie Vale
Jul 3, 1941 – Jan 3, 2012

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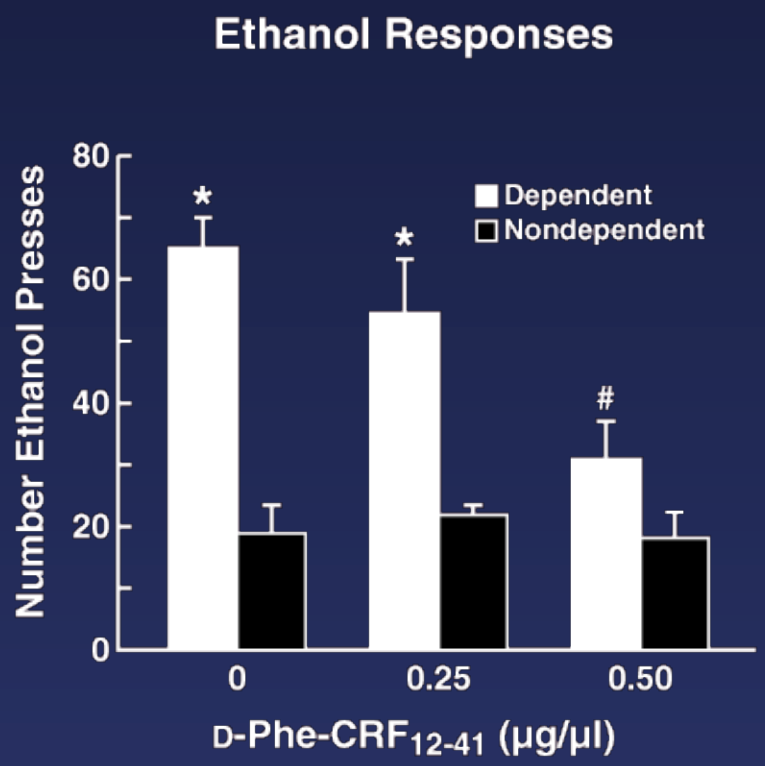
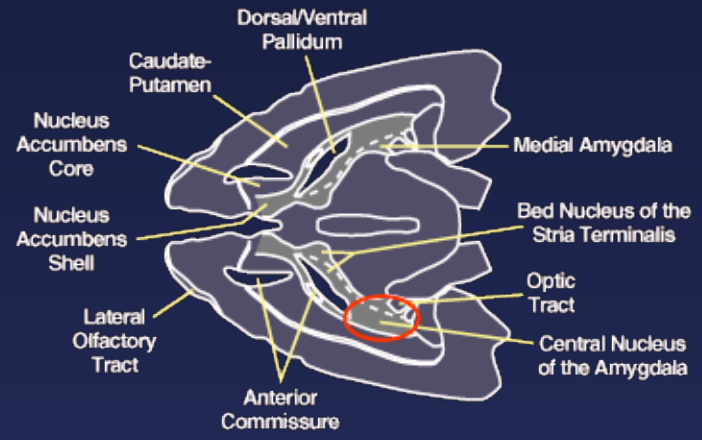
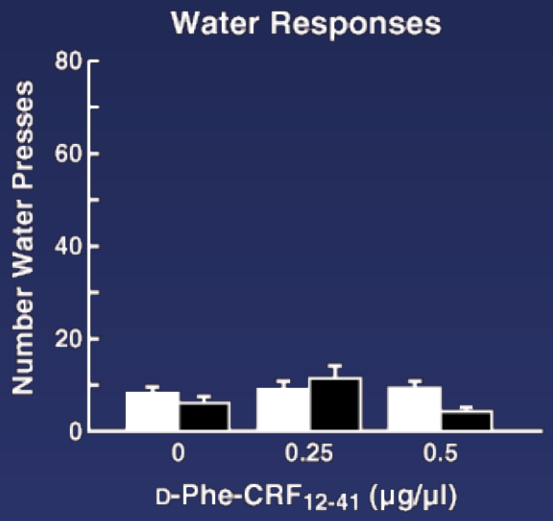
Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ in Central Nucleus of the Amygdala on Ethanol Self-Administration During Withdrawal in Wistar Rats

(30 min session 2 h into withdrawal)







* $p < 0.001$ vs. same-dose, nondependent group

\# $p < 0.001$ vs. dependent, vehicle group

From: Funk C, O'Dell LE and Koob GF. J Neurosci, 2006, 26:11324-11332.

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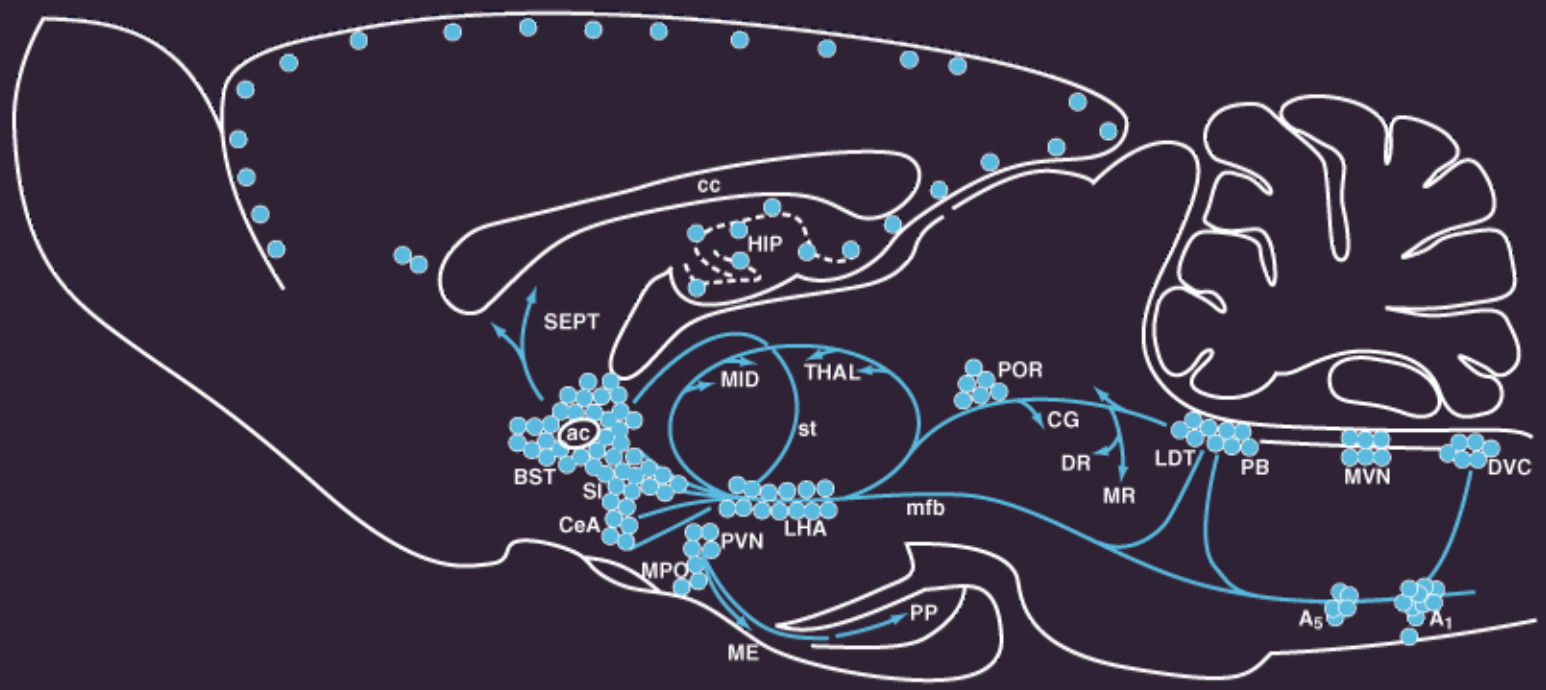
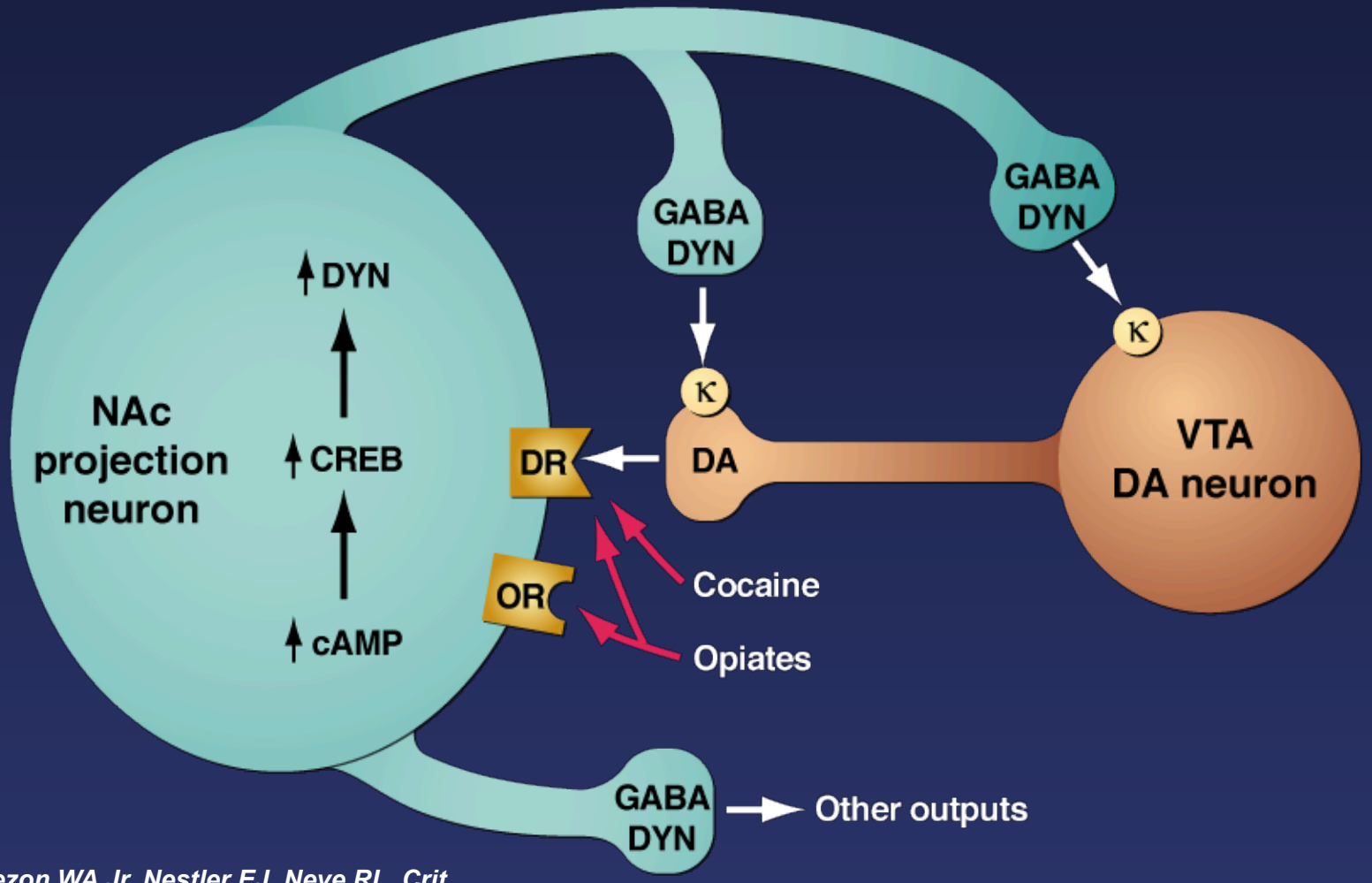
Summary of Drugs of Abuse Interactions with Corticotropin-Releasing Factor Systems



	CRF Antagonist Effects			
Withdrawal-induced changes in extracellular CRF in CeA	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
↑	↓	–	↓	↓

Modified from: Swanson LW, Sawchenko PE, Rivier J and Vale W, Neuroendocrinology, 1983, 36:165-186.
Koob GF, Neuron, 59:11-34

Dynorphin Control of Mesocorticolimbic Dopamine- Within System?



From: Carlezon WA Jr, Nestler EJ, Neve RL. Crit Rev Neurobiol, 2000, 14:47-67.
Nestler EJ. Nat Rev Neurosci, 2001, 2:119-128.

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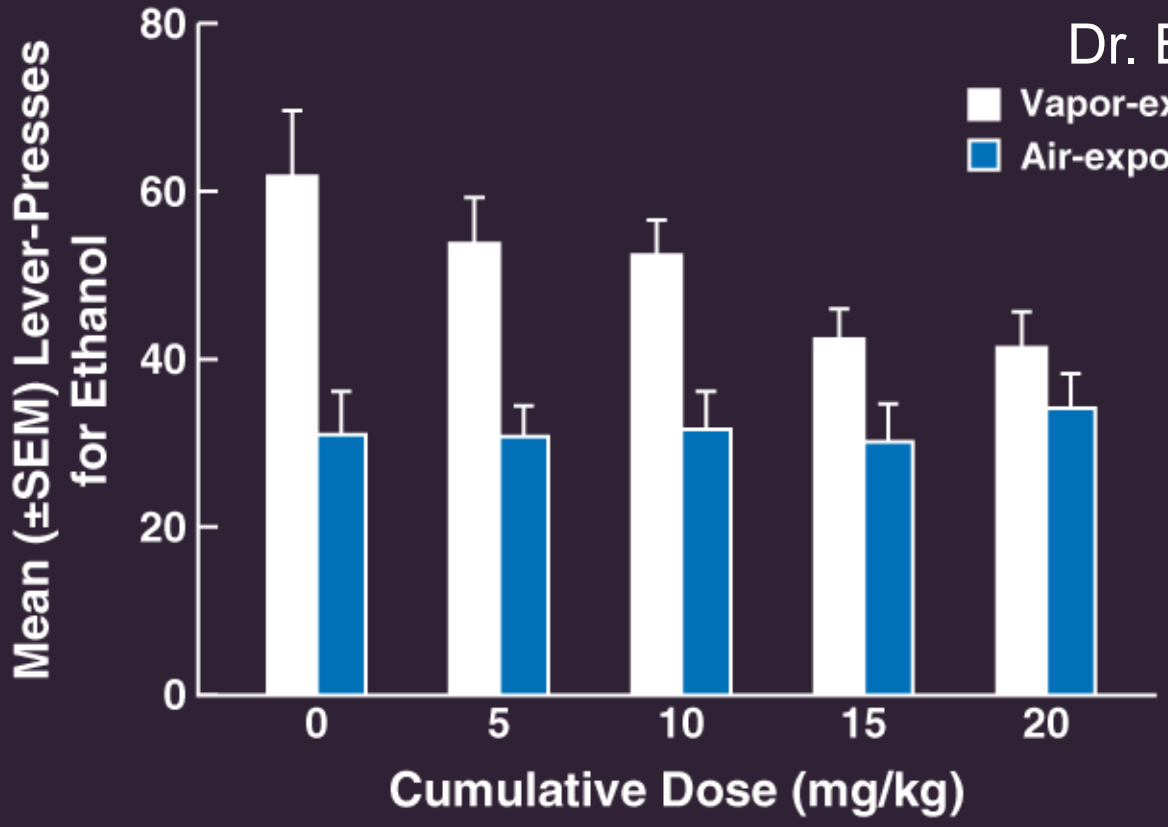
Nor-Binaltorphimine Blocks Dependence induced Increases in Ethanol Self-administration in Rats

Dr. Brendan Walker



From: Walker BM, Zorrilla EP, Koob GF, Addict Biol, 2010, 16:116-119.

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Summary of Drugs of Abuse Interactions with κ-Opioid/Dynorphin Systems

κ-Opioid Antagonist Effects

Withdrawal-induced changes in dynorphin peptide and prodynorphin mRNA in NAc	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
↑	↓	↑	↓	↓

Modified from: Khachaturian H, Lewis ME, Schafer MKH and Watson SJ, Trends Neurosci, 1985, 8:111-119.

Koob GF. Neuron, 2008, 59:11-34.

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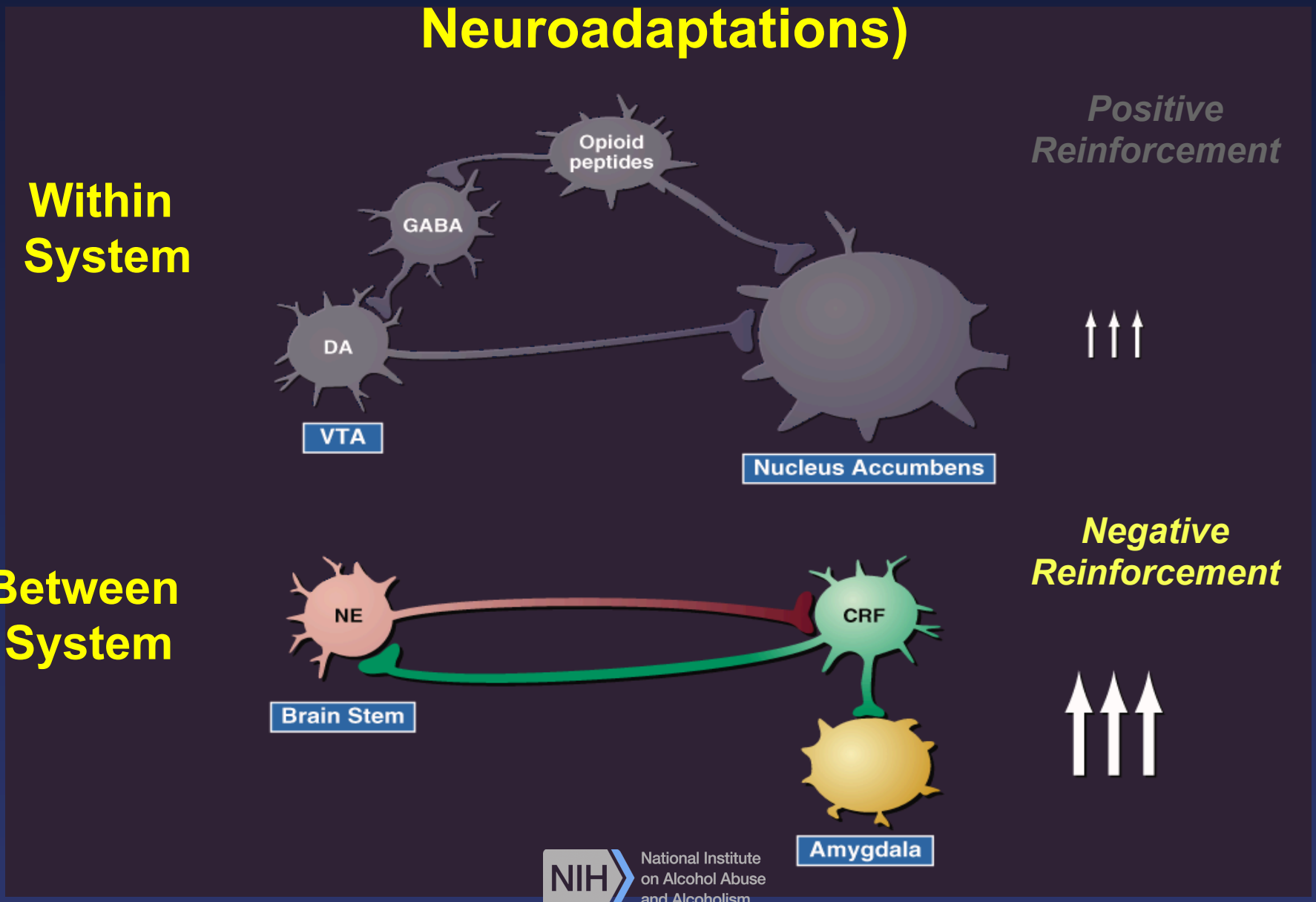
Reward/Stress Neurocircuitry in the Transition to Dependence (Within and Between System Neuroadaptations)



Brain Arousal-Stress System Modulation in the Extended Amygdala

↑ Corticotropin-releasing factor

↑ Norepinephrine

↑ Vasopressin

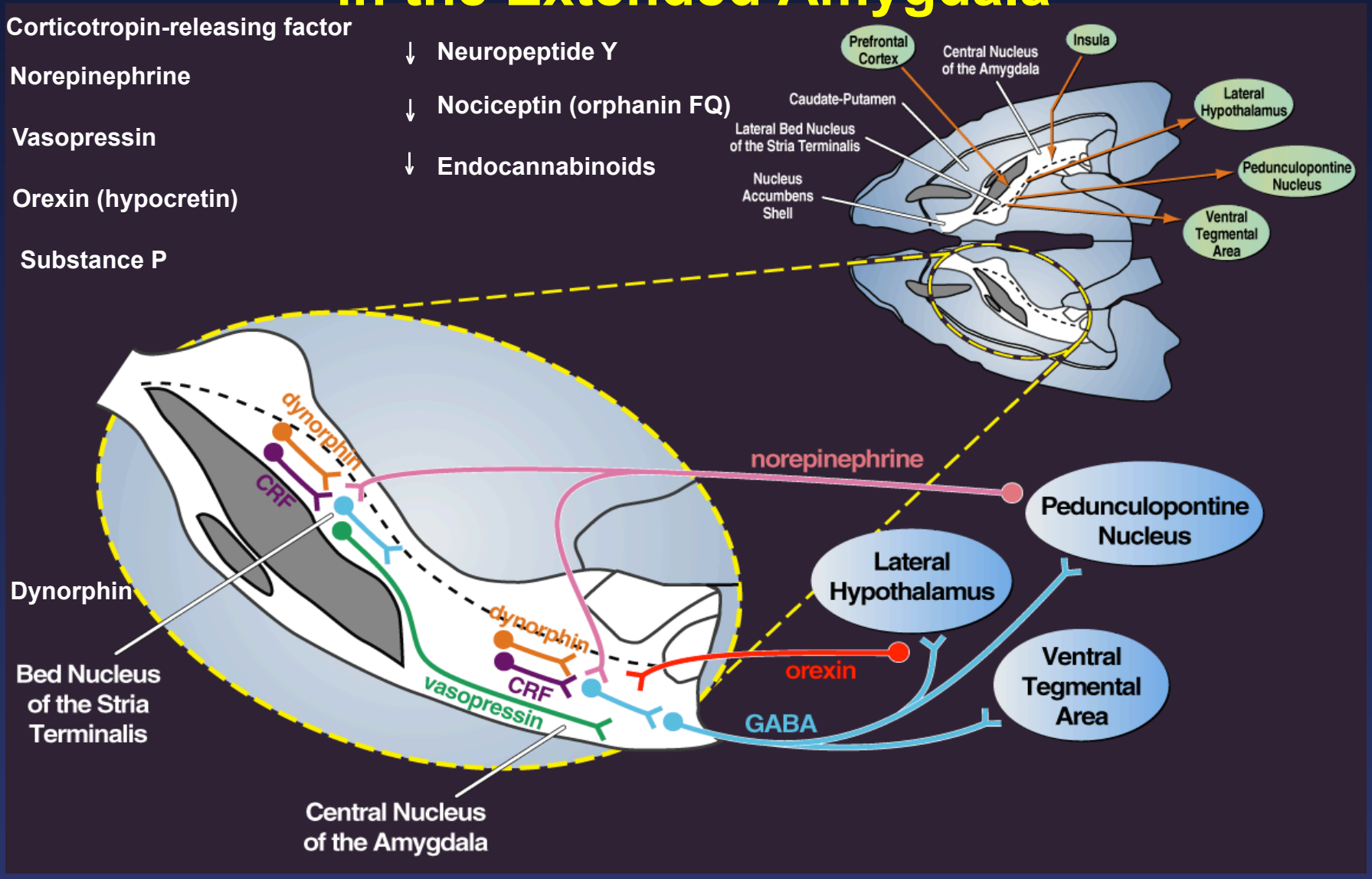
↑ Orexin (hypocretin)

↑ Substance P

↓ Neuropeptide Y

↓ Nociceptin (orphanin FQ)

↓ Endocannabinoids



From: Koob, G.F. 2008 Neuron 59:11-34

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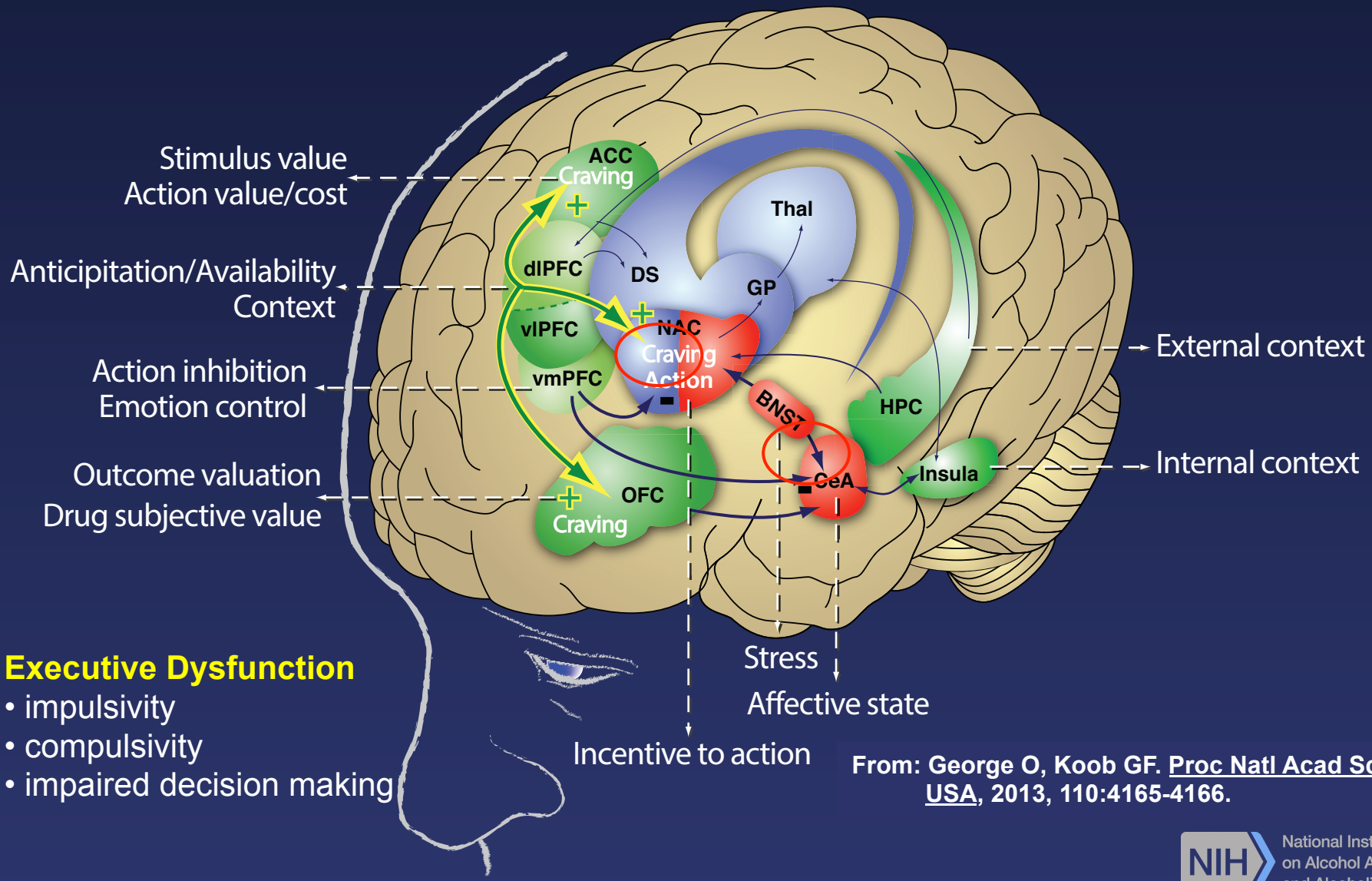
Neural Circuits Controlling Impulsivity and Compulsivity



Executive Dysfunction

- impulsivity
- compulsivity
- impaired decision making

From: George O, Koob GF. Proc Natl Acad Sci USA, 2013, 110:4165-4166.

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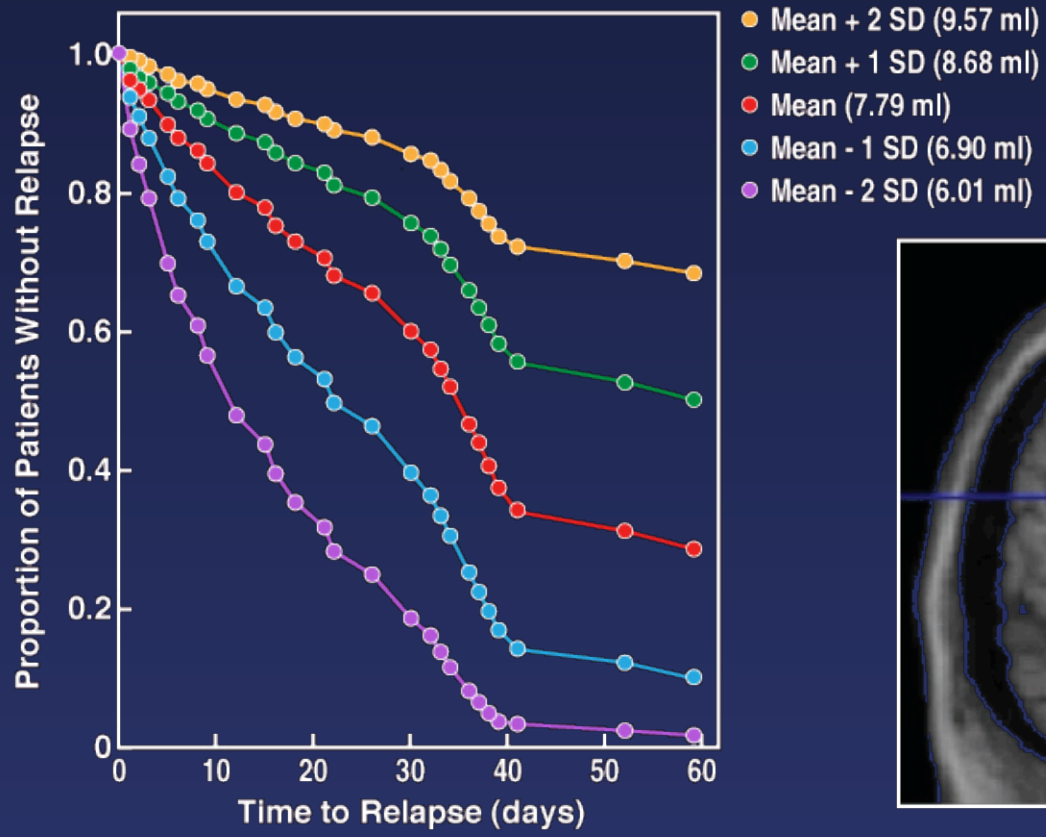
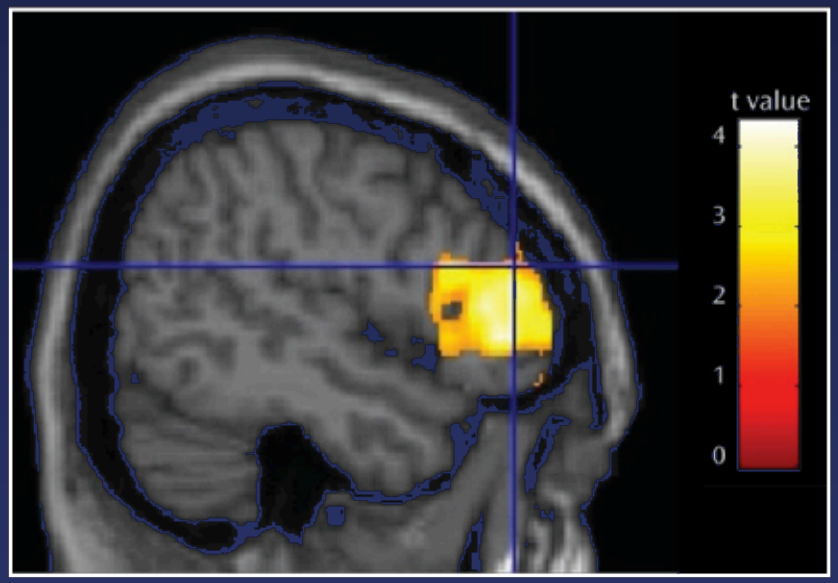
Gray Matter Volume Deficits Predict Time to Relapse in Alcohol-Dependent Patients





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From: Rando K, Hong K-I, Bhagwagar Z, Li C-S R, Bergquist K, Guarnaccia J, Sinha R. Am J Psychiatry 168:2, February 2011

Loss of Control Over Intake: Role of PFC and Executive Control

Dr. Olivier George

Escalation of drug intake

Neuron/oligodendrocyte death

Prefrontal Cortex Abnormalities/ Hypofunction

Impairment of Executive Control

Cause

PFC CRF/GABA interneurons

Withdrawal

PFC DA/NE?

VTA CRF Neurons?

Initial intake

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Bottom Line

1. Addiction is an incentive salience disorder

2. Addiction is a reward deficit disorder/ Addiction is a stress surfeit disorder

4. Addiction is an executive function disorder

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Conclusions

1. **Conceptual Framework for Addiction:** Alcoholism is a syndrome of compulsive alcohol seeking composed of multiple stages and a "hijacking" of multiple sources of reinforcement

2. **Binge/Intoxication Stage:** Brain Reward Circuits. Early neuroadaptations in nucleus accumbens and basal ganglia involve activation of incentive salience and habit formation via activation of dopamine and opioid peptide systems.

3. **Withdrawal/Negative Affect stage:** Brain anti-reward systems. Reward system deficits (decreases in dopamine and opioid peptide function) and brain stress system recruitement (increases in CRF and dynorphin brain stress function) in the extended amygdala.

5. **Preoccupation/Anticipation Stage:** Executive function deficits. Neurocircuitry changes in frontal cortex may contribute to impulsivity and compulsivity via dysregulation of glutamatergic systems.

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Thank You!

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Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health